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Report

The Chemokine SDF1a Coordinates Tissue Migration through the Spatially Restricted Activation of Cxcr7 and Cxcr4b

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Summary

Tissue migration is a collective behavior that plays a key role in the formation of many organ systems [1–3]. Although tissue movements are guided by extrinsic cues, in many contexts, their receptors need to be active only at the leading edge to ensure morphogenesis [4–8]. This has led to the prevalent view that extrinsic signals exert their influence by controlling a small number of leader cells. The zebrafish lateral-line primordium is a cohesive cohort of over 100 cells that is guided through CXCR4-SDF1 signaling [9–11]. Recent work has shown that Cxcr4b activity is only required in cells at the very tip, raising the question of what controls cell behavior within trailing regions [6]. Here, we present the first mutant in zebrafish SDF1a/CXCL12a and show, surprisingly, that the resultant phenotype is stronger than a null mutation in its cognate receptor, Cxcr4b, indicating the involvement of other SDF1a receptors. A candidate approach identified Cxcr7/RDC1, whose expression is restricted to cells behind the leading edge. Morpholino knockdown of Cxcr7 leads to a novel phenotype in which the migration of trailing cells is specifically affected, causing tissue stretching, a defect rescued by the reintroduction of wild-type cells specifically at the back of the primordium. Finally, we present evidence that Cxcr4b and Cxcr7 act independently to regulate group migration. We provide the first example where a single extrinsic guidance cue, SDF1a, directly controls the migration of both leading and trailing edges of a tissue through the activation of two independent receptors, CXCR4b and CXCR7.

Results and Discussion

By performing a large-scale forward-genetic screen for regulators of lateral-line morphogenesis, we identified one mutant, named *medusa*, that displays a highly penetrant recessive phenotype in which posterior lateral-line neuromasts are strongly reduced in number or completely absent (Figure 1A). In vivo time-lapse analysis revealed that although the primordium in *medusa* embryos is specified normally and the constituent cells are motile, the tissue is unable to migrate in a coordinated manner (Figure S1A and Movie S1 in the Supplemental Data available online). This phenotype is similar to that observed in embryos mutant for the chemokine receptor Cxcr4b; however, genetic complementation excluded the possibility that *medusa* encodes a new allele of Cxcr4b. The transplantation of cells injected with SDF1a mRNA was sufficient to stimulate the directed migration of *medusa* mutant primordia to ectopic locations (n = 10, Figure S1B), indicating that the activity of the chemokine guidance cue was abrogated. We directly sequenced the SDF1a coding region in *medusa* mutants and identified a G→A base change creating a premature stop at codon 33 that removes the last two-thirds of the 99 amino acid protein (Figure 1B) and deletes two antiparallel β sheets and the C-teminal helix shown to be essential in Cxcr4 binding [12]. Therefore, by performing a forward screen for defects in lateral-line migration, we have isolated the first mutation in zebrafish SDF1a.

Loss-of-function mutations in either SDF1a or its receptor CXCR4b lead to a similar defect in the guided migration of the lateral-line primordium [10, 11], consistent with the previous finding that they form a monogamous signaling-pair in mouse [13–16]. However, by carefully comparing the lateral-line migration phenotype in both, we arrived at the surprising conclusion that the defect in SDF1a mutants is stronger than in the previously isolated Cxcr4b mutant allele, which is considered to encode a functional null [17]. SDF1a mutants show a complete absence of forward lateral-line migration, the strongest phenotype so far described (Figures 1C and 1D). By contrast, in a subset of *cxcr4b* embryos, the primordium migrates a short distance along the normal path, albeit trailing far behind wild-type migration (Figures 1C and 1D). This suggests that the primordium maintains a degree of SDF1a responsiveness even in the absence of Cxcr4b.

We next searched for chemokine receptors that might mediate this residual activity in *cxcr4b* mutant embryos. Recent work has demonstrated that cells derived from mouse Cxcr4 mutants display significant SDF1-binding activity because of the expression of another chemokine receptor, Cxcr7 (formerly known as the orphan receptor RDC1) [18]. Furthermore, expression of Cxcr7 has recently been described to allow SDF1-mediated chemotaxis in lymphocytes in vitro [19]. Blasting the zebrafish genomic database revealed the presence of a single zebrafish Cxcr7 homolog, which has 57% amino acid identity and 73% similarity to the human protein (Figure S7A). Interestingly, Cxcr7 is not at all present at the leading edge but is restricted to cells in the trailing part of migrating primordium and the deposited neuromast and interneuromast cells (Figure S2). Two-color in situ hybridization shows that although the expression domains of Cxcr4b and Cxcr7 are broadly complementary, there is a region of significant overlap (Figure 2A).

We next addressed the functional requirement for Cxcr7 in lateral-line migration by injecting CldnB::lynGFP embryos with morpholino oligonucleotides designed to knock down Cxcr7 function. Because the Cxcr7 coding sequence is contained in a single exon, both

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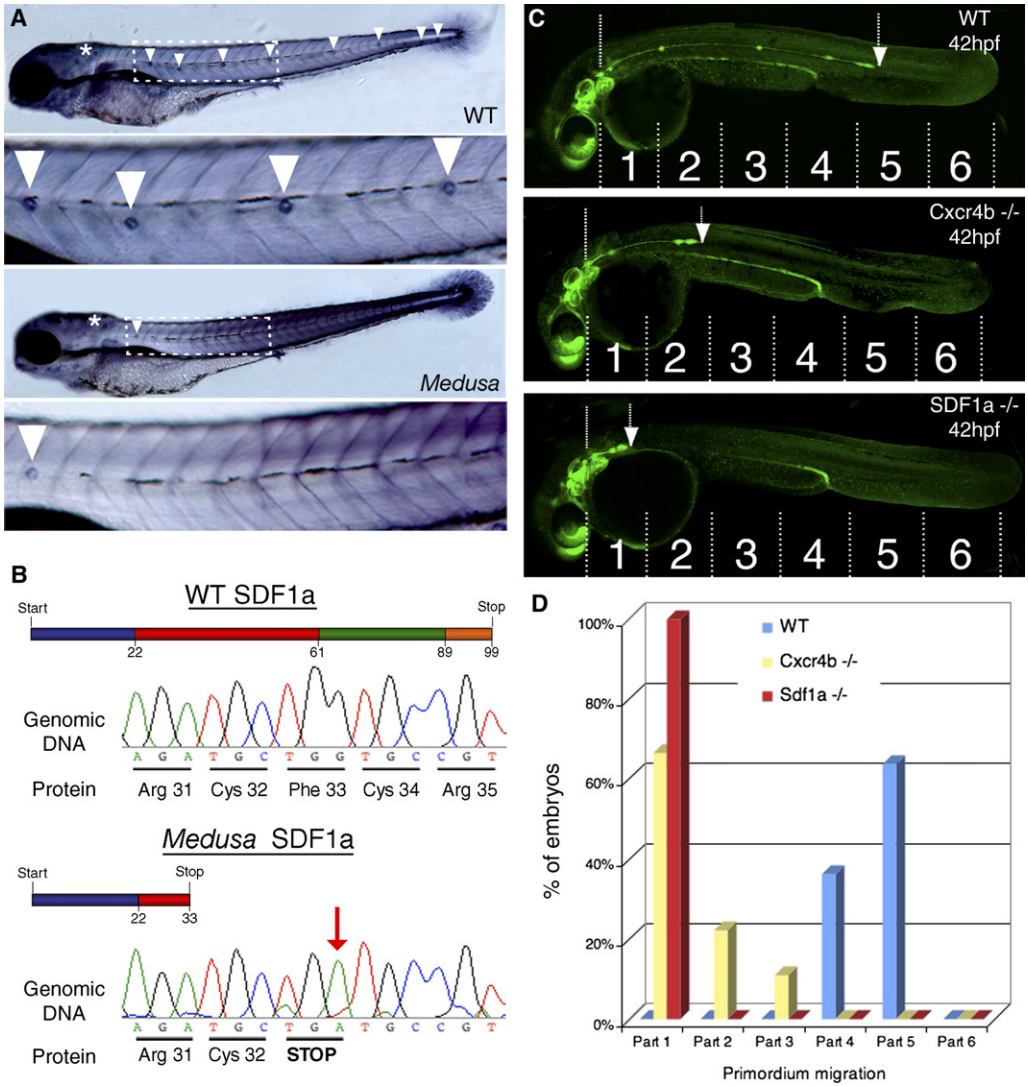

Figure 1. Loss of SDF1a Leads to a Stronger Phenotype than Loss of Cxcr4b

(A) Neuromast deposition was detected at 4.5 days postfertilization (dpf) by alkaline phosphatase staining. Wild-type embryos show a zebrafish-specific neuromast pattern (upper panels, overview and magnified view of dashed box). In *medusa* mutants, the neuromast number in the posterior lateral line is reduced (arrowheads), whereas anterior neuromasts are still present (asterisk) (lower panels, overview and magnification of dashed box).

(B) Schematic representation of a full-length SDF1a protein in the wild-type and a mutated SDF1a protein in *medusa* mutants (the colors represent the four exons of the *sdf1a* gene). A point mutation at nucleotide position 99 converts phenylalanine into a stop codon (red arrow). This nonsense mutation truncates SDF1a after 32 amino acids in *medusa* mutants.

(C) The lateral-line-primordium migration was analyzed in wild-type, *cxcr4b*, and *sdf1a* mutant embryos at 42 hpf. Six equal sections from the ear to the end of the tail were defined, and an equal number of embryos (n = 37) were classified according to the leading-edge position of the primordium (arrows).

(D) Quantification of results from (C) shows that SDF1a mutants have a stronger migratory defect than do *cxcr4b* mutants (compare red and yellow bars).

morpholinos were designed to block translation of the protein. Coinjection with morpholino-resistant and -sensitive Cxcr7-GFP fusion proteins confirmed that these morpholinos efficiently and specifically block Cxcr7 expression (Figure S4). Injection into Cldnb::GFP embryos showed that both give a very similar, highly penetrant phenotype in which migration of the primordium is strongly abrogated. Importantly, embryos injected with a 5 bp mismatch control morpholino show completely normal lateral-line migration (Figures 2B and 2C). Removing the activity of both Cxcr4 and Cxcr7, made possible by the injection of Cxcr7MO into *cxcr4b* mutant embryos, results in a lateral-line-migration phenotype that is similar in strength to that observed in SDF1a mutant embryos (compare Figure 2C with Figure 1C). A similar additive phenotype was seen when morpholinos against Cxcr4b and Cxcr7 were coinjected, resulting in a stronger migration defect than injection of either morpholino alone (Figure S5).

We carefully analyzed the behavior of the primordium during earlier migration stages in Cxcr7 morphants (Figure 3). At 30 hr postfertilization (hpf), in the majority of *cxcr7* morphant embryos, cells in the leading region of the primordium extend in the normal direction of migration, indicating that directionality has not been affected in the absence of Cxcr7 (60%, 23/40). However, time-lapse

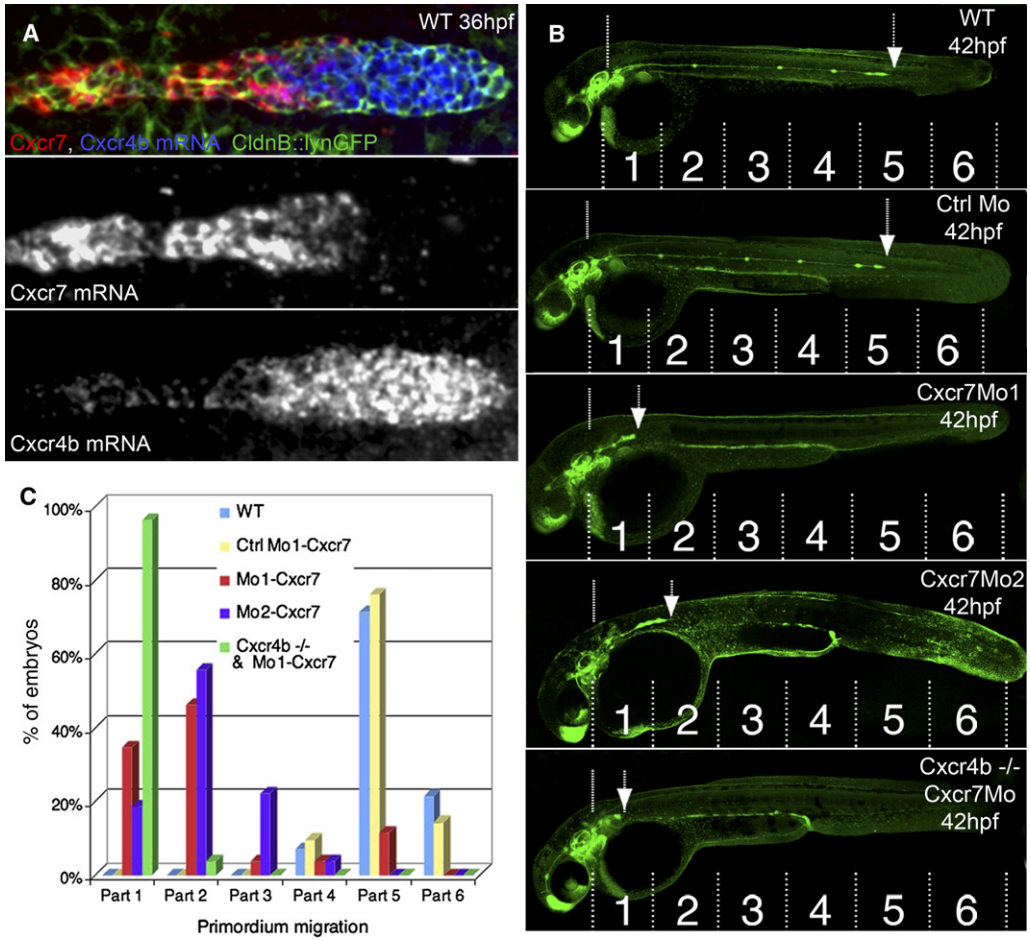

Figure 2. The Zebrafish Homolog of Cxcr7/Rdc1 Is Essential for Primordium Migration

(A) Fluorescent in situ hybridization of Cxcr7 and Cxcr4b in the wild-type CldnB::lynGFP background at 36 hr postfertilization. The middle panel shows the restricted expression pattern of Cxcr7 at the back of the primordium and in the deposited chain cells. The lower panel reveals Cxcr4b expression in the whole primordium.

(B and C) Quantification of primordium migration (as in Figure 1C) in wild-type embryos, wild-type embryos injected with control morpholino (Control Cxcr7Mo, 1 mM), or two morpholinos against Cxcr7 (Cxcr7Mo1, Cxcr7Mo2, 1 mM), and *cxcr4b* embryos injected with Cxcr7Mo1. Wild-type and control morpholino-injected embryos migrate at a similar rate (blue and yellow bars). Primordia treated with the two morpholinos against Cxcr7 (red and purple bars) stop preferentially in part 2; only a few reach parts 3 and 4 or halt already in sector 1. Injection of Cxcr7Mo1 in *cxcr4b* embryos recapitulates the *sdf1a* mutant phenotype (green bars, compare Figure 1D).

imaging shows that cells behind the leading edge are uncoordinated and actively extend protrusions in many directions (Figure 3A, Movie S2). This difference in migratory potential leads to a pronounced stretching of the tissue, a novel phenotype that is clearly distinct from the tumbling behavior observed in *cxcr4b* mutants [6]. Not only does the overall tissue morphology appear stretched, but measurement of cell length reveals that those in the leading edge of Cxcr7 morphants extend to approximately double the length of their wild-type equivalent (Figure S6A). Similar elongated cell morphology has been described in single migrating cells in which rear-end retraction is blocked. A second phenotype observed is the splitting of the primordium; this presumably results from the leading edge tearing free from the remainder (Figure 3C). Once again, this phenotype, which is never observed in either *cxcr4b* or *sdf1a* mutants, is indicative of the inability of trailing cells to migrate efficiently. Finally, a subset of primordia shows a clear rounded morphology (30%, 11/40). Intriguingly, the relative proportion of primordia of this class increases significantly when older specimens are examined, rising from 30% to 60% of the total, whereas the number of stretched primordia falls from 60% to 20% (Figure S6B). Time-lapse imaging confirms that after stretching for several hours, many elongated primordia retract and adopt a rounded morphology (Figure 3B, Movie S3). Although we have no clear explanation for this behavior, studies in single cells have shown that events at the opposing ends are coupled, with leading-edge extension feeding back on trailing-edge retraction and vice versa [20]. Importantly, expression of keratin 15, a differentiation marker for deposited neuromasts and interneuromast cells (http://zfin.org), is indistinguishable in wild-type and Cxcr7Mo embryos, ruling out the possibility that loss of this chemokine receptor affects posterior "fate" (Figure 3D, Figure S3). We next addressed the extent to which these receptors influence each other's expression by carrying out a comprehensive set of in situ hybridizations in the various mutant and morphant

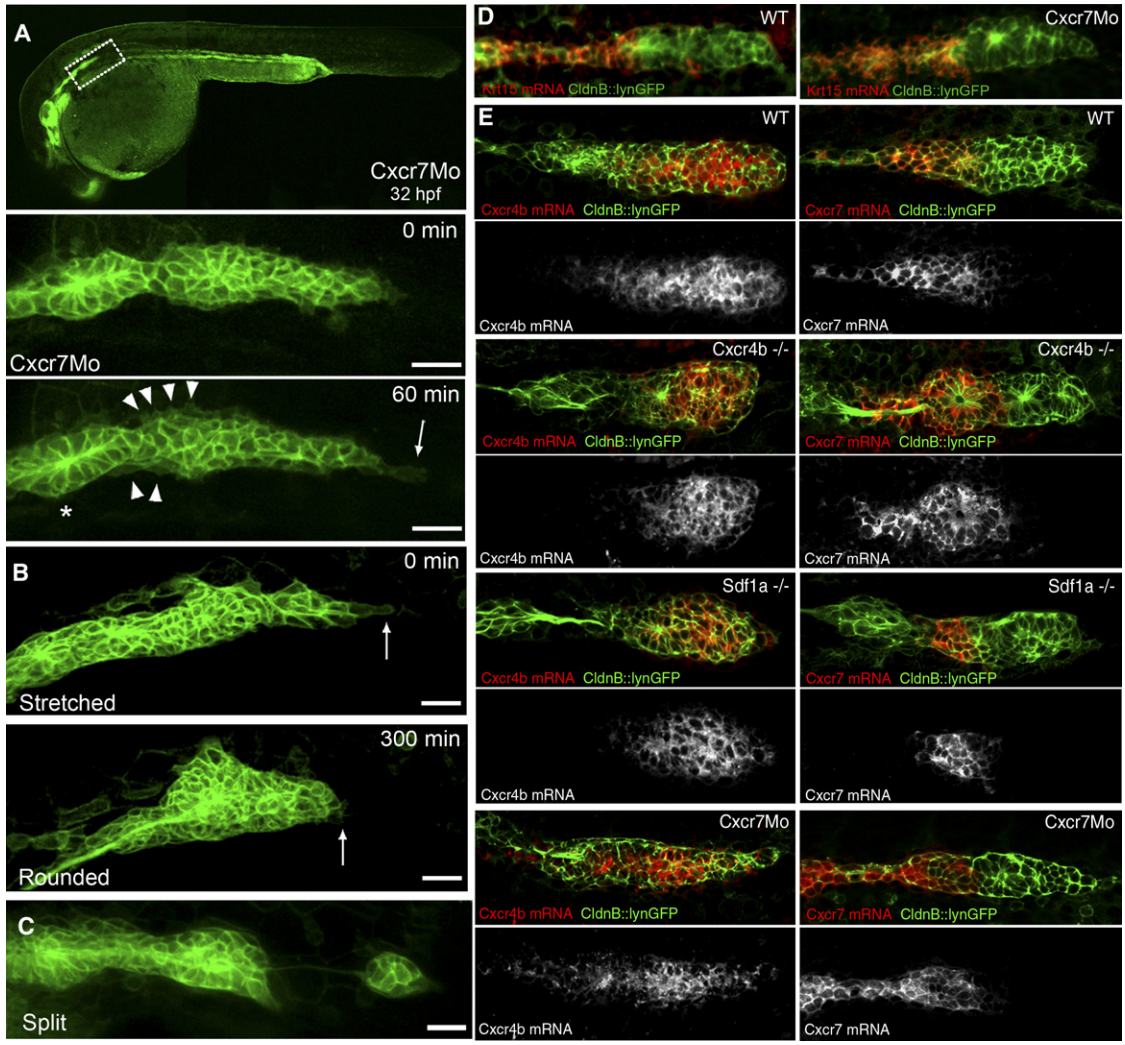

Figure 3. Phenotypic Analysis of Primordium Behavior after Cxcr7 Knockdown

(A) Representative example of a Cxcr7 morphant primordium of the stretched class. The upper panel shows a 10× overview at 32 hpf. Below: frames taken from a 1 hr time-lapse movie (40×) that shows a stretched primordium, which does not migrate. The asterisk indicates the deposited cells, the arrowheads show cell motility at the rear of the primordium, and the arrow depicts the stretching of the leading cells. The scale bar represents 20 μm. A kymograph confirms that tip cells dynamically elongate and retract and indicates that cells within the tissue are motile but do not move (Figure S5A).

(B) Time-lapse analysis of a Cxcr7 morphant embryo at 32 hpf showing the conversion from a stretched to a rounded primordium in 300 min. The arrows show the behavior of the leading cells.The scale bar represents 20 μm.

(C) Example of a Cxcr7 morphant embryo at 34 hpf where primordium splits. The scale bar represents 20 μm.

(D) Fluorescent in situ hybridization of krt15 in wild-type and Cxcr7 morphants at 36 hpf. Expression of krt15 is restricted to the rear of the primordium and to the deposited chain cells in both cases.

(E) In situ hybridization of Cxcr4b (left panel) and Cxcr7 (right panel) in wild-type, *cxcr4b* mutant, *sdf1a* mutant, and Cxcr7 morphant embryos at 36 hpf. Although the morphology of the primordium varies between genotypes, it is clear that the relative expression domains of Cxcr4b and Cxcr7 are unaffected in the different backgrounds.

contexts. Because primordium morphology is also affected by loss of chemokine signaling, embryos were counterstained with CldnB::lynGFP. Surprisingly, this analysis revealed that the loss of Cxcr4b or SDF1a does not result in a significant forward shift of Cxcr7 expression, nor does the loss of Cxcr7 or SDF1a cause a significant rearward shift in Cxcr4b expression (Figure 3E). We conclude that receptor activity is not sufficient to define the expression domains of these two chemokine receptors within the lateral-line primordium.

The restricted expression domain and phenotype resulting from morpholino knockdown suggest that Cxcr7 acts specifically in cells that trail behind the leaders to allow them to respond to external SDF1a. We confirmed the spatial requirement for this receptor by transplanting wild-type cells into Cxcr7 morphant embryos. The presence of transplanted wild-type cells was able to efficiently rescue the migration defect in Cxcr7Mo-injected embryos (n = 9/12, Figures 4A and 4C). However, here, the rescue of migration was only observed in those embryos containing wild-type cells at the rear of the primordium, whereas wild-type clones at the leading edge had no effect (n = 4/4, Figures 4B and 4C). This result is essentially the converse of what is observed in *cxcr4b*

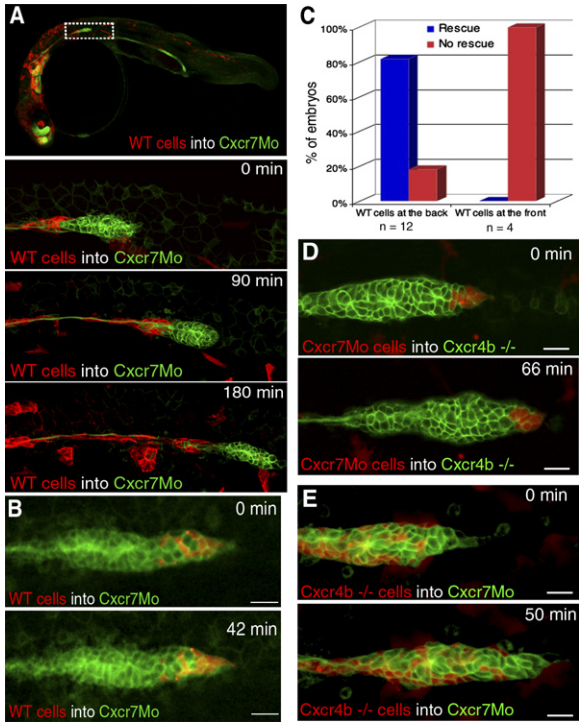

Figure 4. Genetic Mosaic Analysis Reveals Spatially Restricted Requirements for Cxcr7 and Cxcr4b during Lateral-Line Primordium Migration

(A) A 10× overview of wild-type cells (red labeled, lyn-dtTomato mRNA) transplanted into a Cxcr7 morphant embryo at 34 hpf. Time-lapse analysis of a Cxcr7 morphant primordium displays a contiguous clone of wild-type cells in the trailing region. Migration of the primordium is efficiently rescued only up until the point when wild-type cells are deposited. The scale bar represents 20 μm.

(B) Time-lapse analysis of a Cxcr7 morphant revealing that wild-type cells transplanted at the leading edge of the primordium cannot rescue the migration of a Cxcr7 morphant embryo. The scale bar represents 20 μm.

(C) Embryos were screened for the localization of wild-type cells inside the morphant primordia (at the back or at the front). Migration of rescued primordia similar to that of the wild-type was observed in those cases with large clones of cells at the back but not at the front of the primordium.

(D) Time-lapse analysis shows that clones of Cxcr7 morphant cells can efficiently rescue migration of *cxcr4b* mutant primordia. Donor embryos were kept to ensure that Cxcr7 was efficiently knocked down in transplanted cells. The scale bar represents 20 μm.

(E) Rhodamine labeled *cxcr4b* mutant cells were transplanted into Cxcr7 morphants. Transplanted wild-type cells rescue the migration defect of Cxcr7 morphant primordia when present in the trailing regions of the primordium. The scale bar represents 20 μm.

mutants, in which cells at the leading edge rescued but cells at the rear had no effect [6]. Interestingly, because cells in the trailing region are continually being laid down in order to deposit mechanosensory-organ precursors and interneuromast chain cells, these mosaic primordia shed their rescuing Cxcr7-expressing cells. In every case, the shedding of red wild-type cells resulted in the immediate halting of rescued primordium migration. We conclude that continued Cxcr7 activity is required specifically at the rear of the primordium to ensure persistent forward migration of the tissue.

We next turned our attention to the interdependence of these two chemokine receptors in this system. Cxcr7 morphant cells proved to be indistinguishable from wild-type cells in terms of their ability to rescue the migration defect in *cxcr4b* mutants (n = 8), indicating that the presence of Cxcr4b is sufficient to allow detection of the SDF1a stripe by cells in leading regions (Figure 4D, Movie S4). More intriguing is the situation at the trailing edge of the primodium, where both genes are coexpressed. We tested the requirement of Cxcr4b in this region by transplanting *cxcr4b* mutant cells into Cxcr7 morphant embryos. Similarly to the previous experiment, Cxcr4b-deficient cells rescue directed migration with a similar efficiency as do wild-type cells, when present at the rear of Cxcr7 morphant primordia (Figure 4E, Movie S5). We conclude that Cxcr4b and Cxcr7 are sufficient to mediate SDF1a-signaling in spatially distinct domains of the same migrating tissue.

Here, we show that knockdown of Cxcr7 activity leads to a defect in zebrafish lateral-line migration, representing an in vivo requirement of this receptor in a SDF1-dependent process. One major question that arises from this finding is why distinct regions of the tissue use different receptors to respond to the same guidance molecule. While this manuscript was under revision, Dambly-Chaudiere and colleagues published a paper [21] that described morpholino knockdown of Cxcr7 in the lateral line, however with different results and conclusions. They propose that Cxcr7 acts as a nonsignaling receptor whose role is to inhibit Cxcr4b expression in trailing regions and that Cxcr4b-activity conversely represses Cxcr7 expression in leading regions of the primordium. They propose a model in which the function of Cxcr7 is to generate a gradient of Cxcr4b transcription across the primordium that ensures its directional migration. However, by performing a complete expression analysis in our mutants and morphants, we could find no evidence for such a mutual antagonism of expression by these two receptors (Figure 3). Furthermore, although we certainly cannot exclude the possibility that Cxcr7 somehow modulates Cxcr4b-activity, we have presented several pieces of in vivo data that suggest a Cxcr4b-independent requirement for Cxcr7 during lateral-line migration. Loss of Cxcr7 enhances the migration defect in both *cxcr4b* mutants and morphants, resulting in an additive phenotype that resembles our *sdf1a* loss-of-function mutant. Furthermore, live imaging of Cxcr7 morphants reveals a novel phenotype in which the front of the primordium extends in the direction of migration, indicating that overall directionality is maintained. However, cells at trailing edge move randomly and project extensions in all directions, supporting the idea that Cxcr7 is required for trailing cells to detect and extend along the SDF1a stripe. What remains unclear is whether SDF1a elicits qualitatively different responses via the activation of either Cxcr7 or Cxcr4b in this context. Recent in vitro work has shown that the binding of Sdf-1 to Cxcr7 does not elicit the Ca^{2+} mobilization characteristic of Cxcr4-activation [18]. Furthermore, although the T cell chemoattractant Cxcl11/I-TAC can bind to both Cxcr3 and Cxcr7, a Ca^{2+} release and MAP-kinase activation are not observed when it is bound to Cxcr7, suggesting that this receptor does not signal through a classical GPCR pathway [22]. At the cell motility level, it should be noted that cells of the primordium within these two expression

domains show clearly different migration behaviors, arguing that downstream responses may differ. Leading-edge cells, whose guidance depends on Cxcr4b alone, migrate at constant pace, halting only when they reach the end of the embryo. Cells entering the trailing Cxcr7 domain, on the other hand, decelerate before being deposited as neuromasts and their connecting chain of interneuromast cells. These latter cells converge and extend on the SDF1a path, a behavior that is specific for trailing-edge cells and does not require Cxcr4b. Placing these rear-end events under the control of Cxcr7 would therefore provide an elegant way of uncoupling the migration of trailing cells from the leading edge while ensuring that they are deposited along the SDF1a stripe.

Previous work on tissue migration has understandably focused on events at the leading edge [4–8]. Here, we demonstrate that different tissue regions are under differential genetic control at the level of guidance receptor, a result that encourages a more holistic approach to the study of this complex process. This work represents an important step toward understanding a logistical problem that lies at the heart of many morphogenetic events, namely, how large numbers of cells can move as a coordinated tissue while allowing autonomous behaviors within the group.

Supplemental Data

Experimental Procedures, seven figures, and five movies are available at http://www.current-biology.com/cgi/content/full/17/12/1026/DC1/.

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Accession Numbers

The GenBank accession number for the Cxcr4b mRNA sequence reported in this paper is NM_001083832.